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Amyl Nitrite,

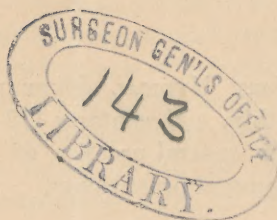
A Powerful Cardiac Stimulant.

BY

EDWARD T. REICHERT, M.D.

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EDITED BY

FRANK P. FOSTER, M. D.,

PHYSICIAN FOR DISEASES OF WOMEN TO THE OUT-PATIENT DEPARTMENT OF THE NEW YORK HOSPITAL.

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AMYL NITRITE, A POWERFUL CARDIAC STIMULANT.

By EDWARD T. REICHERT, M. D.,

FORMERLY DEMONSTRATOR OF EXPERIMENTAL THERAPEUTICS AND INSTRUCTOR IN EXPERIMENTAL
PHYSIOLOGY IN THE POST-GRADUATE COURSE OF MEDICINE IN THE UNIVERSITY
OF PENNSYLVANIA.

THE action of digitalis on the heart was, for many years, invested in doubt, and it was a disputed point between two factions of therapeutists as to whether it was a cardiac stimulant or a cardiac depressant, and it was not until the experimental therapeutist came to the foreground, with his convincing evidence, that this vexed question was finally decided, and the drug placed in its proper physiological classification. The amyl nitrite seemed prone to undergo a similar controversy, for, on looking over the literature on the subject, opinions are found which are as diverse as they well could be, and deductions made which are inconsistent with the results of experiments, and contrary to facts revealed by a more thorough consideration. Wood ("Therapeutics," 1879, p. 348), after studying carefully the experimental papers accessible, concludes that "the whole evidence seems to show that the sudden, thumping, rapid stroke of the heart which is so clearly produced by the nitrite of amyl in man is due, at least in part, to a depression of the inhibitory cardiac nerves"; and, in a previous paper, he gives as another factor the diminished oxidation the nitrite causes, and a thrill of impending suffocation and accelerated pulse due thereto; but this will be referred to more fully later in my paper.

While this statement is in the main correct, because there can be no doubt that the nitrites both depress the inhibitory appa-

ratus and diminish oxidation, yet I believe that there is still another and more important factor, therapeutically, concerned in this increase of the heart's action, as was stated in a recent paper on the potassium nitrite ("Am. Jour. of the Med. Sci.," July, 1880), in which I claimed that the nitrites, in small or moderate doses, acted as *direct* cardiac stimulants, and, moreover, gave the results of a series of experiments with the above-mentioned salt, and endeavored, while discussing its physiological action, to clearly show wherein the deductions of certain observers of the action of the amyl compound had been erroneously drawn, and why the results of certain of the experiments undoubtedly corroborated my belief. I have accordingly resumed a discussion of the subject and have carefully reviewed the accessible papers in this relation, and will consider the evidence deduced under two heads—physiological and clinical.

Referring to the physiological papers, we find that Pick ("Centralbl. f. d. med. Wissensch.," Berlin, 1873, No. 55) declares that it causes a relaxation of the heart muscle, and that the accelerated action of this organ is, in part at least, due to the opening of the vascular channels; that Filenhe (Pflüger's "Archiv," Bd. ix, p. 490), by the result of a single and very interesting experiment, indicated that the increase of the cardiac heat was due alone to a depression of the vagi nerves, for it was found in this experiment that after section of these nerves, an electric current being employed by direct application to the peripheral portion of the severed trunks, of such a strength as to lower the pulse rate to the normal, the increase did not occur as in normal animals; that Mayer and Friedrich ("Arch. f. exper. Path. u. Pharm.," 1875, v, p. 55) in a different way corroborated Filenhe's testimony, for they observed that sudden asphyxia did not slow the pulse after the administration of the nitrite as it did in normal animals, and, moreover, when they pressed the carotids, and prevented the blood from gaining access to the cerebral arteries, the increase did not occur, nor did they find any diminution of the pulse rate by endeavoring to induce a reflex inhibition of the heart by irritating a sensory nerve.

Wood ("Am. Jour. of the Med. Sci.," 1871, 1, p. 422) states that, so far from being a cardiac stimulant, it is a direct depressor of the circulation, because, although it increases the number of the beats, it never increases the force; and in a later and more elaborate article, based upon the results of a direct series of experiments on animals (*ibid.*, 2, p. 39), concludes that it "does not act upon the heart until a considerable point of saturation of the blood and system is reached," and that the heart is then depressed (p. 53).

He did not at this time make any experiments directly to decide what the cardiac action of the poison was, except in determination of the local action on the exposed heart of the frog in *toxic* amounts, when he found, after placing a few drops on that organ, that its action speedily became arrested. In a more recent article (*ibid.*, 1871, 2, p. 359) a discussion of the subject is resumed, and he theoretically explains the "excited, violent, and labored action" of the heart in this way: "when the nitrite is taken into the lungs it instantly arrests or diminishes oxidation, and a thrill of impending suffocation runs through the system, in obedience to which the respiratory and circulatory systems gather up and exert to the utmost their forces. The central impulse sent to the cardiac and respiratory muscles is at first much more than sufficient to overcome any direct action of the nitrite upon them, but, the inhalation being persisted in, the impulse is constantly growing weaker, and the direct influence of the drug stronger, so that there soon comes a time when the reverse is true, and the heart's power is more or less nearly extinguished."

Dugau ("Rev. Mens. de Méd. et de Chir.," July, 1880; quoted in "London Med. Record," Aug. 15, 1880, and "Am. Jour. of the Med. Sci.," Oct., 1880, p. 554) concludes, from the result of an elaborate series of experiments, that the nitrite acts upon the heart after all the nerves have been severed; that strong doses cause a diastolic arrest, and that the acceleration of the heart beat seems to be in relation with the fall of arterial tension, *for it occurred after all nervous connection of the heart with the central nervous system was severed*. Brunton ("Med. Times and Gaz.," 1870, i, p. 320) found that the nitrite did not diminish the work done by the heart in a given time, although it decidedly increased the frequency of its contractions. The frequency he is inclined to attribute to a depression of the inhibitory nerves, because it was more apparent in dogs, in which the vagal apparatus is more sensitive than in rabbits ("Jour. of Anat. and Physiol.," v, 1871, p. 92); but he did not make any experiments to specially determine how the pulse was affected, and his deductions, as may be inferred, are based upon theoretical grounds alone. In experiments on the blood pressure he found the same decided diminution as is noted by other observers, but in seven experiments in which the aorta was compressed immediately below the diaphragm the pressure was not reduced as in normal animals, for *a primary rise occurred which equaled about one fifth the normal*, and which preceded a marked fall. Moreover, in three other experiments, in which the spinal cord was cut and the aorta compressed as before, a similar result was recorded. He

concludes that the diminution of the arterial tension was vaso-motor and not cardiac, but, unfortunately, he does not discuss the cause of the increase in animals with the aorta compressed.

In reviewing the results above recorded, and the deductions made therefrom by the different investigators, we find, indeed, quite a diversity of opinion to deal with. If we first consider the theories of the *modus operandi* of the action on the pulse, much in the papers of Filenhe, Mayer and Friedrich, and Brunton goes to show that the nitrite does depress the vagal apparatus and increase the pulse in this way; yet, evidently, this does not cover the ground, according to Pick's opinion, nor those of Wood and Dugau. Although experimenters almost universally agree that the heart is ultimately slowed and paralyzed, yet, as we see, they do not agree as to how the frequency is affected, and when we come to examine their papers it is found that Filenhe, Mayer and Friedrich, and Dugau were the only ones who made experiments in direct determination of this point, and the deductions of the first three observers must be accepted with allowance because of the very indirect, but no less ingenious, way in which they sought to decide this action. Yet it seems we must admit that the vagi apparatus is depressed, and that the increased action of the heart is at least partially in this way effected. Wood's theory is indeed a beautiful and masterly one, and well worthy of my illustrious friend and teacher, but, unfortunately, it has been founded rather upon hypotheses than direct experimentation. Pick's is logical enough, for it is a truism that there is a compensatory relation existing between the action of the heart and the condition of the vaso-motor system, and that when the vascular channels are open the heart will naturally beat faster in endeavoring to overcome the excessive drainage, and *vice versa*. Dugau's view closely coincides with this, but where he was misled was in not isolating the action on the vaso-motor system from that on the heart, as we shall presently see.

Regarding the action on the arterial pressure, it is almost universally conceded that the marked diminution is both vaso-motor and cardiac, the latter factor coming in late in the poisoning, as is believed by both Wood and Brunton. If this is so, it must be certain that the early fall of pressure is entirely vaso-motor.

If, now, it were possible to eliminate the action of the nitrite on the heart from its action on the vaso-motor system, we could readily determine just how far the acceleration of the heart's beat was affected by this diminution of pressure occurring from vaso-motor dilatation, as well as determine how the amount of work done by the heart is influenced. This identical thing was done, although

imperfectly, in Brunton's seven experiments when he pressed the abdominal aorta immediately below the diaphragm, and in the three later ones, in which he compressed the aorta and made section of the spinal cord; for it must be certain that, when the aorta was firmly pressed upon, the action of a large portion of the vaso-motor peripheries was practically paralyzed, because they were unable any longer to affect the arterial tension, and this was even further increased in the animals in which a section of the cord was made, which, of course, practically annihilated the vaso-motor centers in the medulla oblongata. Now, it must be equally as clear that, if we thus have the action of the vaso-motor system practically abolished, and the disturbing influences of the respirations or struggles overcome by curarizing the animals, as was also done, any change in the arterial tension which occurs will be the resultant of a direct cardiac action. What was the result in each of these ten experiments? In every one of them there was a primary and marked rise of pressure, which equaled as much as a fifth of the normal. It, therefore, must be apparent that this curious change in the results must be due to a direct cardiac action and an effect of a direct increase of the heart's power. If we now admit Dugau's evidence that the heart's action is increased after severance of all central nervous communication, it is conclusively proved that the increase of arterial tension is due to a direct stimulation of the heart, increasing both its frequency and the amount of work performed. Why Brunton, Pick, and Dugau did not reach a similar conclusion is, it is obvious, simply because they did not eliminate the vaso-motor from the cardiac action. It is also clear from the foregoing that the acceleration of the pulse must also in part be cardiac.

In a paper on the potassium nitrite, previously referred to, I claimed that the nitrites all affected the economy in a similar manner, and that, although it was found that the potassium salt caused a primary rise of pressure preceding the diminution, which was an entirely different result from that obtained on normal animals with the amyl nitrite, yet briefly it was explained in this way—that the nitrites acted in two ways to affect the blood pressure, the one by directly stimulating the heart, and the second by depressing the vaso-motor system, the centers especially; that the stimulating effects on the heart ultimately gave way to depression; and that the reason why the amyl nitrite did not cause a rise of pressure, like the potassium salt, was because its vaso-motor action was comparatively more intense, and was more than sufficient to overcome the stimulant effect on the heart, which was finally indicated to be a fact by a comparison of the results of Brunton's experiments and my own.

It was further clearly demonstrated that the potassium nitrite caused at least a part of the increased frequency of the pulse by a direct stimulation of the heart, and probably by a consentaneous depression of the inhibitory centers.

If, therefore, we accept these deductions as made from the results of Brunton's and Dugau's experiments, it will be obvious that the action of the amyl nitrite is identical with that of the alkaline salts, and, consequently, that it is a direct cardiac stimulant, increasing the frequency of the heart's action and the amount of work done in a given time.

If we now look into the clinical history of this interesting compound, we find that there is no paucity of evidence to support this belief, but, indeed, that cases illustrating it are so numerous that, even without the experimental evidence as above deduced, we could arrive at no other conclusion. For instance: 1, there can be no possible doubt that chloroform is a direct and powerful depressant of the heart, and that in toxic amounts it seriously diminishes the powers of this organ and causes death in a vast majority of cases by this parietic action; 2, that it is a conceded fact that in collapse and syncope the depressed condition of the heart is a marked symptom; 3, that in certain forms of heart disease, whether there be a condition of fatty degeneration, valvular insufficiency without compensating hypertrophy, or simple dilatation, the heart's powers are enfeebled and we have the occurrence from time to time of paroxysms of distress, which are undoubtedly due to a further depression of its working capacity. It is, therefore, evident that in each of the above-mentioned three divisions we have an unmistakable condition of cardiac depression, which, in the last of them, is frequently and decidedly evinced in the paroxysmal attacks which recur from time to time; and it must be apparent that the administration of cardiac depressants in such conditions of the system would be attended with harm, if it did not materially aggravate the symptoms or induce death—for who would think of giving aconite or tartar emetic in cardiac syncope, or when a patient was cold, cyanosed, and gasping for life's breath in a paroxysm of heart pang? * Did the amyl have no further primary effect on the heart than to simply increase its frequency by a depression of the vagi apparatus or by inducing it through a diminution of the arterial tension and without affect-

* An apparent exception to this is the use of hydrocyanic acid, but this is given in such small amounts that only its primary effect on the circulation is obtained, which is a slowing and increased fullness of the pulse, due to a stimulation of the inhibitory nerves, and accompanied by a slight rise in pressure, the depression of the heart and fall of arterial tension being a secondary effect.

ing the amount of work done, it would seem certain that in such cases as above quoted either its value as a therapeutic agent would be *nil*, or else it would even aggravate the symptoms, since its only admitted action on the heart, besides the increased frequency, is a depression of its powers and ultimate diminution of its pulsations.

Now, what does the clinical history teach us of the action of the nitrite in chloroform poisoning? Browne ("Med. Gaz.," June 11, 1870) believes that it seems worthy of a trial in chloroform narcosis because its use is followed by a marked acceleration of the heart and flushing of the face. Boder ("Lancet," May, 1875; quoted in "Proc. of the Med. Soc. of the County of Kings," Brooklyn, N. Y., 1875) gives three cases in which dangerous and alarming symptoms of the effects of chloroform were instantly and effectually overcome. Hinton ("Phila. Med. Times," v, 1875, p. 694) cites another illustrating its stimulant effects; and Burrall ("Lancet," May, 1875), Schüller ("Med. Times and Gaz.," Dec. 12, 1874), and Lane ("Brit. Med. Jour.," 1877, i, p. 101) reiterate this statement. The latter observer concludes that when it is inhaled in small quantities it produces recovery from chloroform insensibility, and that this is due to a removal of the cerebral anæmia by the dilatation of the arterioles, to the raising of the temperature of the body, and the removal of the paralysis of the heart. Solger ("Wien. med. Presse," Feb., 1875) furnishes further evidence of the antagonism of the action of the amyl and chloroform; and Dabney ("Richmond and Louisville Med. Jour.," June, 1874) and Smart ("Detroit Rev. of Med.," x, 1875, p. 661), in experiments on animals, further testify to its efficiency. Dabney states that three animals out of four in chloroform insensibility recovered when death was apparently imminent, and that it produced a decided increase of both the force and frequency of the heart. Further, a very interesting experiment of my own, showing the powerful stimulant effects of the nitrites on the heart, is given in a recent paper on the Ethylene Bichloride ("Phila. Med. Times," May 21, 1880), in which the heart was so seriously depressed that the pulsations were imperceptible to the touch, and the pulse-curve tracing was but a mere streak, no oscillations being apparent; yet after giving the amyl the heart's action was recovered with astonishing rapidity.*

Jones ("Practitioner," vii, 1871, p. 213) gives a case of syn-

* These last references, which properly belong to the physiological papers, are given here because of their bearing such a close relationship to the clinical papers on the same subject.

cope in which the radial pulse was scarcely to be felt, and when the nitrite was given it caused it to beat rapidly and full. From the rapidity with which the patient recovered he concludes that the syncopal condition would have continued longer but for the ether. Minor ("Virginia Med. Monthly," iv, 1878, 1876) used it in a case of locomotor ataxia when the patient was in a condition of impending death, there being a hippocratic expression, stertorous and irregular breathing, complete unconsciousness, an imperceptible cardiac impulse, and cold, clammy extremities. The amyl was given by inhalation, but with no effect, and it was therefore repeated hypodermically, three minims being used; and in a few moments "the heart responded, as evinced by the appearance of a more natural hue of the cutaneous surface. The pulse was recognized in the radial artery. Respiration became better." The temperature was restored, and the patient responded to a pinch, which before was unnoticed. By repeating the dose the pulse became incompressible. As much as fifteen minims was given hypodermically at once. Another exceedingly interesting case is cited by Madden ("Practitioner," xii, 1874, p. 295) of a woman who suffered with severe and intractable menorrhagia, and who at the time referred to in his article was apparently dead. Upon using the amyl nitrite the respirations and circulation became fairly established and consciousness was subsequently restored. Moreover, whenever she appeared to be falling into this collapsed condition the amyl was resorted to with the happiest results; hence, he thinks that this case "shows in a remarkable manner the power which the nitrite possesses to rouse the heart which has almost ceased to beat."

Two cases of fatty heart serve to further illustrate this stimulant action and the beneficial results, as a consequence, from its use. The first is that of Osgood ("Am. Jour. of the Med. Sci.," 1871, 2, p. 360), who found it to act with remarkable efficacy, and so much so that he believes that death would have ensued in a few moments if it had not been given. The second case is one of Janeway's ("N. Y. Med. Jour.," xx, 1874, p. 58), in which, after the complete extinction of the radial pulse, the nitrite caused it to become full. There are also two cases of valvular disease. Wood ("Am. Jour. of the Med. Sci.," 1871, 2, p. 361) states that in his case the effect of the drug in relieving the pang when other remedies failed was astonishing; and Jones (*loc. cit.*) tells us of a woman who suffered from cardiac dyspnoea, with a dilated hypertrophy of both ventricles (the dilatation being in excess), a feeble circulation, extreme anasarca, pulmonary oedema, lividity of the face, and shortness of breath. The use of the amyl nitrite produced most beneficial effects and induced

a pleasant glow all over the body, and on each occasion of its use she felt easier and more comfortable about the chest.

In reviewing all the foregoing facts, I think doubt can no longer exist that the amyl nitrite, like the alkaline salts, acts as a powerful and direct cardiac stimulant, increasing both the frequency of the heart's pulsations and the amount of work done in a given time.

106 HALSEY STREET, NEWARK, N. J., June, 1881.

